Technology Assessment Program

Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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Appendix 3

Systematic Review: PET as a Diagnostic Test in Head and Neck Cancer

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Appendix 3

Systematic Review: PET as a Diagnostic Test in Head and Neck Cancer

The final literature database searches for the systematic reviews were performed on September 10, 1996; the assessment represents peer-reviewed literature published and indexed as of that date.

This Appendix to the PET assessment presents the results of the systematic review of PET in head and neck cancer. A general rationale for the use of PET in oncology is supplied by Hawkins, et al. (1994) and Hoh, et al. (1994):

- many forms of cancer characteristically perturb tissue biochemical and physiological processes and PET imaging can be expected to detect the resulting abnormalities;
- reliance on tumor histology and anatomy limits the oncologist's tools for selecting optimal treatment;
- the ability to monitor metabolic responses to treatment could allow the early re-direction of therapy in patients who fail to respond to the first attempt at radiation or chemotherapy.

These and other authors (e.g., Price and Jones, 1995) report that PET studies in cancer are emerging as a major focus of the technology, both in basic research and in clinical investigations. Information gathered by the MDRC Technology Assessment Program from VA PET facilities corroborates that perception (see *Appendix 9: Experience With PET in VHA*).

Fluorine-18-fluorodeoxyglucose (FDG) is the most commonly employed radiopharmaceutical in PET cancer studies. Many neoplasms have high glycolytic rates, resulting in intracellularly trapped phosphorylated FDG that can be imaged with PET. Hawkins, et al. (1994), note that tumor-specific biochemical characteristics of glucose transport and phosphorylation may affect quantitative estimates of tumor glucose metabolism with FDG PET, and that investigations are under way to define these characteristics. However, these uncertainties may be of less concern with qualitative or semiquantitative FDG PET cancer studies because the primary intent of such studies is to detect and map tumor foci, not to rigorously quantify tumor glycolytic rates.

In some instances, PET imaging techniques have been modified to meet the needs of cancer diagnosis. Most PET systems allow axial fields of view (the length of the body encompassed by a series of cross sectional images) of approximately 10 cm. Cancer is frequently distributed beyond this field of view, and whole body image acquisition procedures have been developed (Hoh, et al., 1993). Since it is impractical to apply standard transmission scanning attenuation correction methods to these procedures, whole body PET imaging is primarily useful as a qualitative indicator of disease distribution.

Nieweg (1994) and Price and Jones (1995) define a number of potential applications for PET in oncology. These include:

- tumor detection (although PET images offer insufficient structural detail and should not be used to visualize anatomy; registration techniques to combine PET and anatomic imaging into a single image are under development to circumvent this limitation);
- staging (particularly using whole-body imaging methods) although there is a lower limit to the size of metastases that can be detected by PET;
- detection of local recurrence of disease, since anatomically-based imaging is often limited by the effects of treatment;
- prediction of tumor response to chemotherapy;
- treatment monitoring.

I. BACKGROUND

A. General sources

This overview is based on Vokes, et al. (1993), and on information distributed by the National Cancer Institute (NCI) through its on-line Physician Data Query (PDQ) system (accessed in September, 1996). Additional sources are cited in the text and included in the "References" section.

B. Description

This report will define head and neck cancer as the common squamous-cell carcinomas of the oral cavity, nasal cavity and paranasal sinuses, pharynx, and larynx. Skin, brain, ocular, thyroid, and salivary gland tumors and the rare tumors of other histopathologic types (sarcomas and lymphomas) that can have primary sites in the head and neck will not be discussed.

C. Epidemiology

Approximately 41,000 incident cases of head and neck cancer (3% of incident cases of all types of cancer), and 12,500 deaths (2% of all cancer related deaths) attributable to head and neck cancer are estimated for the United States in 1996 (American Cancer Society, 1996). Within the Veterans Health Administration, malignant neoplasms of the lip, oral cavity, and pharynx (but not larynx) accounted for a total of 3,361 hospital patients discharged (0.4% of all patients discharged within the system), with an average length of stay of 21.3 days, in fiscal year 1994 (Annual Report of the Secretary of Veterans Affairs, 1994).

Both incidence and mortality rates for head and neck cancer are substantially higher among men than among women (Spitz, 1994). Spitz (1994) reports that the incidence of oral and pharyngeal cancers decreased in white men of all ages from 1973 to 1989. However, there have been significant increases in incidence among black men; the incidence rates among black men is nearly double that of white men for those younger than 65 years, as are mortality rates.

The most important risk factors for all head and neck cancers are tobacco and excess alcohol use. Additional exposures that have been found to be associated with head and neck cancer include marijuana, occupational exposures (nickel refining, woodworking, the textile industry), and some viruses (particularly Epstein-Barr virus for nasopharyngeal cancer). Although sporadic cases of head and neck cancer occur in young adults and nonusers of tobacco and alcohol, most cases occur in males over 50 years of age with these risk factors.

D. Diagnosis

Mucosal surfaces in the upper aerodigestive tract, lungs, and esophagus are exposed to the same carcinogens, and multiple anatomic sites may be at risk for the simultaneous or sequential development of dysplastic and malignant lesions ("large field carcinogenesis"). Accordingly, there is a high incidence (in some reports as high as 25 to 30%) of synchronous (occurring at the same time) and metachronous (occurring later in time) second primary cancers in the head and neck, lung, and esophagus. Diagnostic, staging, and follow-up procedures are designed to monitor patients for second primaries as well as for the extent of the first tumor.

The signs and symptoms of head and neck cancer vary with the primary site and the stage of disease. Patients with early stage cancer may have only vague, nonspecific symptoms, and diagnosis requires a high index of suspicion among primary care physicians, oral surgeons, and general dentists. Higher stage disease is associated with increasingly severe symptoms at presentation. Some patients present with enlarged cervical lymph nodes but without an apparent primary mucosal surface tumor.

Initial diagnosis of head and neck cancer is based on physical examination, biopsy, indirect laryngoscopy or examination with a flexible fiberoptic nasopharyngoscope, radiologic evaluation (computed tomography or magnetic resonance imaging), and endoscopic examination (direct laryngoscopy, esophagoscopy, and bronchoscopy) with the patient under anaesthesia. Neither a liver-spleen scan nor a bone scan are generally felt to be of significant diagnostic value.

E. Staging, treatment, and survival

The TNM (tumor, node, metastasis, illustrated below) staging system integrates all clinical and imaging information, including the size of the primary lesion, involvement of adjacent structures and lymph nodes, and distant metastases. As in all malignancies, the stage of disease at diagnosis is a primary prognostic factor, with lower stage, locally confined disease associated with a higher probability of cure after treatment and longer survival than higher stage disease.

Table 1: Head and Neck Cancer TNM Staging System

	N_0	N_1	N_{2-3}	
T_1	I			Roman numerals represent stages
T_2	II			All M_1 tumors are stage IV
T_3		III		
T_4			IV	

T stages are separately defined for each anatomic region.
N_0-N_3 indicate a range of cervical lymph node involvement, from clinically negative to nodes > 6 cm.
M_0 indicates the absence of metastatic disease at distant sites; M_1 indicates its presence.

Approximately one-third of patients with head and neck cancer have lower stage, confined disease at diagnosis; most of the remaining patients have locally or regionally advanced disease (including spread to lymph nodes in the neck). Head and neck cancer which has already metastasized widely (e.g., to brain, lung, bone, or liver) at the time of presentation is less frequent. Standard therapy accordingly emphasizes local and regional approaches (surgery, radiation therapy, or both) with curative intent. With the exception of laryngeal cancer (for which induction chemotherapy may be used with radiation in an attempt to circumvent the need for laryngectomy), chemotherapy is generally accepted as standard therapy only for patients with recurrent or metastatic disease. In such patients, the intent of chemotherapy is palliative, rather than curative.

Table 2 Head and Neck Cancer: Stage of Disease, Standard Therapy, and Survival by Primary Site

Primary Site	Stage of Disease	Standard Therapy	5 Year Survival (3 year where noted)
All head and neck primary tumors	I II III or IV Inoperable, III or IV	Surgery or radiation Surgery or radiation Extensive surgery (including neck dissection) followed by radiation Radiation alone, sometimes followed by surgery	> 80% > 60% < 30% 2-25%
Nasal cavity/paranasal sinuses	I II III IV	Surgery and radiation Surgery and radiation Surgery and radiation Surgery and radiation	60-70% 60-70% 25-35% 10-25%
Nasopharynx	I II III IV	Radiation Radiation Radiation, followed by neck dissection as indicated Radiation; neck dissection for recurrent or persistent nodes	65-95% 50-65% 30-60% 5-50%
Oral cavity	I II III IV	Surgery or radiation, depending on anticipated functional result Surgery or radiation, depending on anticipated functional result Surgery and/or radiation, depending on site Surgery or radiation, depending on size and site of lesion	70-90% 50-80% 25-35% < 25%
Oropharynx	I II III IV	Surgery or radiation Surgery or radiation Surgery with post-operative radiation Surgery with post-operative radiation	60-100%, depending on site 50-100%, depending on site 20-30%, depending on site 14-20%, depending on site
Hypopharynx	I II III IV	Laryngopharyngectomy, occasionally with post-operative radiation Laryngopharyngectomy, occasionally with post-operative radiation Surgery with post-operative radiation Surgery with post-operative radiation	50-80% 50-60% 30-50% 15-25%
Larynx	I II III IV	Radiation Radiation Radiation; laryngectomy if persistent disease after radiation Total laryngectomy and followed by radiation	96-98% 80-94% 3-year, 45-75% 3-year, 10-35%
Metastatic squamous neck cancer with occult primary	 N1 N2 N3	Appropriate evaluation for primary in upper aerodigestive tract, esophagus, lung or genitourinary tract Radiation or neck dissection Radiation or neck dissection Radiation or neck dissection	 3-year survival: 40-50% 25-30% 10-15%
Metastatic/recurrent disease, any primary site	Most treatment failures occur at site of original primary. Metastatic disease = IV	Surgery or radiation as feasible and dependant on first line treatment received Chemotherapy with palliative intent; further investigation into quality of life during chemotherapy needed.	 Response lasts median 3-6 months; 40% of patients who receive combination chemotherapy alive at 9 months

Table 2 presents information on stage of disease at diagnosis, standard therapy, and survival. The NCI notes that there is a paucity of well-designed, controlled prospective studies comparing treatment modalities in patients with head and neck cancer, making it difficult to unequivocally state the ideal therapy for a specific site or stage of cancer originating in this anatomic area. The preferred treatment generally will depend on the skills of the treating physician, the needs of the patient, and a determination of the treatment which will cause the least functional disability. Ongoing clinical investigations for cancers at most sites in the head and neck focus on the addition of chemotherapy to surgery and radiation for local or regionally advanced disease in an attempt to reduce the need for surgical intervention and to improve cure and survival rates.

Since head and neck cancer is strongly associated with tobacco and alcohol use, many patients also have chronic heart, lung, and liver diseases. These comorbid conditions account for approximately 30% of deaths among patients with head and neck cancer. All of these tumors present complex medical, surgical, psychosocial, and rehabilitative problems, which frequently are managed by multidisciplinary groups including head and neck surgeons, radiation oncologists, medical oncologists, speech pathologists, nutritionists, dentists, pathologists, and diagnostic radiologists. Therapy for head and neck cancer inevitably has significant, sometimes profound, side effects, and even patients who are cured are often disfigured, lose their ability to speak and eat normally, and suffer the psychological morbidity associated with these disabilities.

F. Potential roles for PET

Diagnostic tests have an impact at several points in the initial work up and treatment of a patient with head and neck cancer. These include:

- initial diagnosis in the symptomatic patient, the patient with clinical signs of malignancy, or the patient with unexplained cervical lymphadenopathy [which occurs in 3% to 9% of patients with cancer of the head and neck (de Braud and Al-Sarraf, 1993)];

- decision making regarding specifics of treatment (in head and neck cancer patients a significant question is whether to enhance strictly local treatment at the primary site to include treatment of microscopic metastases to the cervical lymph nodes in a clinically negative neck);

- monitoring the results of treatment;

- post-treatment surveillance to define disease recurrence at the original primary site, or to define metastatic spread of disease.

Bailet, et al. (1992) note that CT and MRI have significantly improved the detection of occult cervical metastases in patients with head and neck cancer. Improved detection in turn has resulted in improved management of patients at high risk of cervical metastases (e.g., tumors of the base of the tongue, supraglottic larynx, and pyriform sinus). However, further improvements in the points at which imaging could impact patient management noted in the list above are still sought. Evaluation of head and neck tumors after surgery and/or radiation therapy can be complicated by the effects of treatment, making anatomically-based post-treatment imaging studies difficult to interpret (Chaiken, et al., 1993). Surgery inevitably results in deviations from normal anatomy, and radiation therapy can be associated with loss of tissue planes, edema, and residual masses. In this context, the information supplied by FDG PET on glucose metabolism in head and neck tumors could be clinically useful.

The results of FDG PET imaging in patients with head and neck cancer were first published by Bailet, et al., (1992) from the UCLA School of Medicine and its affiliated hospitals, including the West Los Angeles Veterans Administration Medical Center. This and subsequent studies indicated that FDG PET imaging of primary tumors and related cervical lymph node metastases and assessing tumor response to therapy was feasible. The table below summarizes the qualitative review by Mancuso, et al. (1994), of the initial experience at UCLA:

Potential Benefit of FDG PET	Currently Available Data Suggest...
identification of primary site in patients with cervical lymphadenopathy of unknown origin, allowing for more timelyfocused treatment of the primary. Second, synchronous primaries may be detected.	PET appears to be able to reliably detect primaries (including submucosal) of 1.0 cm and greater diameter; unpublished data indicate that PET can detect up to 50% of inapparent primaries, compared to 15-20% with CT or MRI.
Detection of subclinical cervical lymph node metastases, allowing more informed decisions re observation vs treatment in patients otherwise at low risk of cervical spread.	PET is limited in its ability to detect cervical lymph node metastases. Since FDG uptake is probably proportional to the number of cells in a metastatic lesion, microscopic nodal deposits are likely to produce false negative results. Reactive, metabolically hyperactive nodes may produce false positive results. No anatomic or physiologic study (including PET) is likely, in the near future, to detect microscopic disease accurately enough to make it the sole determinant of treatment of the neck.
Earlier detection of persistent or recurrent tumor, allowing more prompt salvage therapy.	It remains unknown whether PET will allow an earlier definition of treatment failure than CT or MRI. Further studies with longer follow up are needed, as are studies to define high-risk patients who would benefit from intensive post-treatment surveillance. Optimal post-treatment surveillance protocols remain undefined; no surveillance protocols have been demonstrated to be associated with improved survival.

Source: Mancuso, et al., 1994

II. RESULTS

Twenty-three articles were selected from the MEDLINE and other database searches and from the bibliographies of initially retrieved articles as meeting the screening criteria. After review, 9 (39%) were found to meet the criteria for assignment to the following levels of the diagnostic efficacy hierarchy (Fryback and Thornbury, 1991; *Appendix 2: Assessing Diagnostic Technologies*): 4 met the definition of technical efficacy; 4 met some of the evidence-based criteria for diagnostic test evaluations (Table 4), and one additional study met some of the evidence-based criteria while comparing PET to MRI and made an attempt to extrapolate findings to therapeutic efficacy (Table 5). Table 3 summarizes cross-study findings on PET and alternative technologies.

All currently available data on the use of PET in patients with head and neck cancer are based on case series studies, which provide Level V (i.e., the weakest) evidence of any association between the use of a technology and improved patient outcomes. Some studies, however, have internal controls for subsets of head and neck cancer patients (e.g., patients with and without cervical node involvement).

Studies classified at the "technical efficacy" level of the diagnostic efficacy hierarchy (Fryback and Thornbury,1991) are listed in Section VII, below. The definition of technical efficacy was expanded to include studies that were not designed to assess diagnostic accuracy or that did not meet the evidence-based criteria for diagnostic accuracy. These studies did provide information necessary to subsequent diagnostic efficacy studies. Data abstraction tables for technical efficacy studies are on file with the MDRC Technology Assessment Program.

Table 4 abstracts data from the studies that assessed the diagnostic accuracy of PET for certain applications in head and neck cancer; these studies also compared PET directly to other imaging technologies. The diagnostic accuracy data reported in Table 4 apply only to detection of cervical lymph nodes and distinguishing recurrent disease from treatment artifacts. The studies in Table 4 did not include control groups without head and neck cancer or with diseases that need to be distinguished from head and neck cancer, and accordingly did not meet evidence-based medicine criteria for diagnosing primary disease. Table 5 abstracts data from the one retrospective, hypothetical therapeutic efficacy study. The MDRC Technology Assessment Program was unable to locate any studies using PET in head and neck cancer at the patient outcome or societal levels of the diagnostic efficacy hierarchy.

Methodologic and sample size limitations of the studies of PET in head and neck cancer argue for caution in interpreting the sensitivity and specificity reported in Tables 4 and 5. Only one of the studies in Table 4 (Lapela, et al., 1995) blinded image interpreters. It was decided that meta analyses of the diagnostic accuracy studies would not yield further insights into PET's usefulness as a diagnostic test, due to the potential for significant bias in the design of these studies. Qualitative results, organized by the potential role of PET in the management of head and neck cancer, are:

A. Detecting unknown primaries in patients who present with metastatic cervical nodes

The MDRC Technology Assessment Program was unable to locate any PET studies that met evidence-based criteria for diagnosis of unknown primaries.

B. Detecting primary disease

The MDRC Technology Assessment Program was unable to locate any PET studies that met evidence-based medicine criteria for diagnosis of primary disease.

C. Detecting cervical metastases

A number of studies partially met evidence-based medicine criteria for diagnostic test evaluations. One study (Benchaou, et al., 1996) met all evidence-based criteria and received a good methodologic quality score. These studies suggest that PET is somewhat limited in its ability to detect subclinical cervical node metastases: a high rate of false positives for cervical nodes is associated with PET in the studies in Table 4, and is attributed to the metabolic activity of reactive lymph nodes. The available evidence suggests that PET does not perform substantially better in this setting than do MRI, CT, or ultrasound-guided fine needle aspiration biopsy.

One study (Braams, et al., 1995; Table 5) was classified at the therapeutic efficacy level (Level 4, detailed in *Appendix 2: Assessing Diagnostic Technologies*), because the authors extrapolated diagnostic accuracy to a retrospective, hypothetical decision regarding performing neck dissection in their small series of patients. While this study indicates that

PET may impact clinical management and patient outcomes, its small size and hypothetical nature suggest that further documentation would be needed to define marginal benefits over anatomic imaging.

D. Detecting recurrent disease

Lapela, et al. (1995), found that blinded visual interpretation of PET and blinded interpretation of CT had approximately equivalent sensitivity and specificity in detecting recurrent disease. An unblinded study (Rege, et al., 1994) found that PET was superior to MRI in detecting recurrent disease.

III. SUMMARY

Table 3 summarizes published findings on the diagnostic accuracy efficacy of PET and its alternatives in diagnosing cervical lymph node involvement with disease and in evaluating suspected disease recurrence. Only one study (Lapela, et al., 1995) met all evidence-based medicine criteria for diagnostic test evaluations; the unit of analysis in this study was regions, not patients. While data on other uses of PET obtained in uncontrolled studies are also included in Table 3, the MDRC Technology Assessment Program was unable to locate any published studies that met completely evidence-based medicine criteria for evaluations of diagnostic tests for the use of PET in these settings. PET and CT have been compared in one retrospective, hypothetical therapeutic efficacy study, which also supplies diagnostic accuracy information (Braams, et al., 1995). The results of studies that did not blind image interpreters to disease status should be interpreted with caution. All of the studies listed in Table 3 received low methodologic quality grades due to the absence of blinding, the absence of controls, and/or small sample sizes.

IV. DISCUSSION

Authors of studies intended to document diagnostic accuracy generally concede that PET supplies information that can be complementary to, but that does not replace, anatomic imaging information in the management of head and neck cancer patients. In clinical use, PET would be incorporated into a diagnostic test battery, and information on pre- and post-test probabilities of disease at each step in the diagnostic strategy would be needed to define the marginal information yield associated with each of the tests (including PET).

Any analysis of the effect of PET on the outcomes of treatment which might be attempted, based on longer follow up of patients who have been reported in the existing literature, would be further complicated by the wide range of primary sites and stages of squamous cell cancer of the head and neck included in the case series, and the associated, correspondingly wide range of site-specific treatments and outcomes.

Mancuso, et al. (1994), note that FDG PET must be cost competitive with CT and MRI and/or offer a significant increment of improvement in detection if its use is to be justified. Other competing technologies may be under development. Drane, et al. (1994), report a technique which combines FDG with SPECT, and which may be associated with a lower per scan cost than PET and with wider availability. Gamma cameras are under development which permit imaging of 511-keV photons from positron emitters such as FDG. Eighteen patients with head and neck tumors were included by Drane, et al. (1994) in an initial study. However, the reporting of results in the

published report was meager; the authors caution that the study was intended only to support the feasibility of such imaging, not to determine the diagnostic accuracy of FDG SPECT.

Alternative imaging protocols have been proposed in an effort to reduce the number of unnecessary neck treatments in patients with head and neck cancer. Baatenburg de Jong, et al. (1993), report the results of a diagnostic thinking efficacy study. Ultrasonography has a high sensitivity (97%) for detection of metastatic involvement of the neck. The specificity is low (32%) unless it is combined with ultrasound-guided fine needle aspiration biopsy; Braatenburg de Jong, et al., found a specificity of 93% for the combined technique. These authors used pre-test probabilities of disease according to anatomic site (from the literature) and a range of sensitivities and specificities to calculate post-ultrasound-guided fine needle aspiration biopsy probability of disease. Clinicians could apply these results to the treatment threshold probabilities in use at their institutions (e.g. at some institutions all patients with a probability of occult metastases > 5% receive elective neck dissections).

Weiss, et al., (1994) provide guidance concerning treatment thresholds. These authors used decision analysis to plan management for patients with head and neck cancer and clinically negative necks, using clinical staging information and the probabilities of occult cervical metastases associated with each stage. Their objective was to generate an optimal threshold (for the probability of occult cervical metastases) beyond which treatment would be given. Based on their analysis, these authors found that it is reasonable to observe patients with a probability of occult metastases less than 20%, while treatment is warranted in the presence of a probability greater than 20%.

V. SUGGESTIONS FOR FURTHER RESEARCH

The types of study designs, and the strength of the resulting evidence from further research into the role of PET in head and neck cancer care, will be inherently constrained by a number of factors. The epidemiologic data cited earlier in the discussion of head and neck cancers indicate that these cancers are relatively rare, and collecting enough cases of such cancers for some study designs (e.g., prospective or cohort studies) may be difficult.

1) PET has potential uses at several points in the diagnosis and management of head and neck cancer patients. An early step in defining these uses is determination of diagnostic accuracy. Studies that have been published to date generally have methodologic weaknesses, and may overestimate accuracy. Controlled, blinded studies should be conducted; multi-center studies may be needed to accrue meaningful numbers of patients.

2) The role of PET in modifying treatment decisions or improving the outcomes of head and neck cancer therapy is currently limited to one retrospective, hypothetical study with significant methodologic limitations. Prospective studies should be conducted, and again may need to involve multiple centers to accrue meaningful numbers of patients.

3) A VA PET registry could provide a range of data on demographic and clinical characteristics of patients on whom PET studies are performed, and on their clinical outcomes in a variety of settings; While a registry would not provide the strength of evidence associating PET would improved outcomes that would be provided by randomized clinical trials, it would circumvent the problem of low disease prevalence.

4) The role of PET as part of a diagnostic test battery should be defined.

Table 3 Summary of the literature: Diagnostic accuracy efficacy of PET and alternatives in head and neck cancer
(from studies comparing PET directly to other diagnostic tests)

Role	Study	N	Operating characteristics*				Evidence-based medicine criteria**			Methodologic quality grade***
			PET	*CT*	*MRI*	*Other*	*controls*	*standard*	*blinding*	
Unknown primary	Rege, et al., 1994	4 cases 0 controls	Se = 50%		Se = 0%		-	+	-	D
Known primary site	Rege, et al., 1994	30 cases 0 controls	Se = 97%		Se = 77%		-	+	-	D
	Laubenbacher, et al., 1995	17 cases 0 controls	Se = 100%		Se = 100%	endoscopy, Se = 100%	-	+	-	D
Primary tumor staging (size, extent)	Laubenbacher, et al., 1995	17 cases 0 controls	Se = 41%		Se = 41%	endoscopy, Se = 59%	-	+	-	D
Cervical node involvement	Rege, et al., 1994	16 cases 18 controls	Se = 88% Sp = 89%		Se = 81% Sp = 89%		+	+	-	D
	McGuirt, et al., 1995	14 cases 31 controls	accuracy = 82%	accuracy = 82%		clinical exam accuracy = 71%	+	+	-	D
	Laubenbacher, et al., 1995	83 pos nodes 438 neg nodes	Se = 90% Sp = 96%		Se = 78% Sp = 71%		+	+	-	D
		18 pos neck sides 16 neg neck sides	Se = 89% Sp = 100%		Se = 72% Sp = 56%		+	+	-	D
	Braams, et al., 1995	22 pos nodes 177 neg nodes	Se = 91% Sp = 88%		Se = 36% Sp = 94%		+	+	-	D
	Benchaou, et al., 1996	54 pos node groups 414 neg node groups	Se = 72% Sp = 99% PPV = 89% NPV = 99%	Se = 67% Sp = 97% PPV = 74% NPV = 95%		clinical exam Se = 61% Sp = 97% PPV = 72% NPV = 95%	+	+	+	B
Suspected recurrent disease	Rege, et al., 1994	10 cases 7 controls	Se = 90% Sp = 100%		Se = 67% Sp = 57%		+	+	-	D
	Lapela, et al., 1995	16 pos 17 neg	Se = 88 -94% Sp = 43 -86% depending on criteria for pos	Se = 92% Sp = 50%			+	+	+	C

Abbreviations:
Ct, computed tomography
MRI, magnetic resonance imaging
neg, negative for disease
pos, positive for disease
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value
US/FNA, ultrasound/fine needle aspiration

* operating characteristics defined in Appendix 2: Assessing Diagnostic Technologies, pages 5-7
** Appendix 2, page 8
*** Appendix 2, page 9

Table 4 Diagnostic accuracy efficacy of FDG PET and anatomic imaging in detecting cervical lymph nodes from head and neck cancer

Notes *All of the studies in the table are cases series (Level V evidence); most of the studies did not meet evidence-based medicine criteria for evaluations of diagnostic tests for primary head and neck cancer (because no patients without head and neck cancer were included). However, there were internal controls for subsets of patients (e.g. those with cervical lymph nodes positive for disease), and it was possible to calculate sensitivity and specificity for PET in those subsets.*

Some of the studies in the table also do not meet the evidence-based medicine requirement for blinding; sensitivity and specificity reported in these studies should be interpreted with caution.

Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Studies reviewed but not included are listed in Section VIII.

The reference test for the PET operating characteristics reported in the "Results/Comments " column is biopsy.

Study	***Patients/Methods***	***Results/Comments***
Rege, et al., 1994 *UCLA School of Medicine, West LA VAMC*	**Purpose** • to summarize cumulative (3 year) experience with PET as a supplement to anatomic imaging in H&N tumors • PET and MRI compared to histopathology **Cases** 60 patients with biopsy-proven H&N cancers (53 SCC, 7 other types) recruited after presenting for evaluation of H&N tumors: • 34 patients scanned before treatment (staging); 15 of these received serial scans to monitor response to treatment; 4 had unknown primary tumors and metastatic cervical nodes • 19 patients evaluated for recurrent disease • 7 patients with advanced disease receiving palliative laser therapy (not included in analyses) **Methods** • all patients received MRI and PET • MRI interpreted by 2 experts with full clinical information available • PET interpreted visually by consensus of 3 nuclear medicine experts • FDG uptake in tumor/nodes compared to cerebellum • MRI used as anatomic template to locate increased FDG uptake seen on PET **Limitations of study design** • Images interpreted without blinding • blood glucose status of patients not noted	**Staging/cervical nodes (16 cases with + nodes, 18 cases with - nodes):** • PET: *Se = 87.5%; *Sp = 89%; *PPV = 87.5%; *NPV = 89% • MRI: *Se = 81%; *Sp = 89%; *PPV = 87%; *NPV = 84% **Patients evaluated for recurrent disease (10 cases confirmed by histopathology; 7 cases negative histopathology for PET, 6 for MRI):** • PET: *Se = 90%; *Sp = 100%; *PPV = 100%; *NPV = 87.5% • MRI: *Se = 66.7%; *Sp = 57%; *PPV = 66.7%; *NPV = 57% **Cervical metastatic nodes/unknown primary (4 cases, no controls):** • PET identified primary disease in 2/4 patients • MRI negative in 4/4 **Detecting known primary (30 cases, no controls):** • PET detected known primary in 29/30 patients • MRI detected known primary in 23/30 patients **Treatment monitoring:** some patients experience transient increase in FDG uptake during treatment **General findings:** • PET supplies information which is complementary to, but does not replace, MRI and CT anatomical information in the management of H&N cancer patients • reactive lymph nodes/inflammation may cause false-positive PET results

Study	*Patients/Methods*	*Results/Comments*
McGuirt, et al., 1995 *Bowman Gray School of Medicine*	**Purpose** • to examine ability of PET to detect metastatic tumor in cervical nodes • to compare PET and standard diagnostic methods **Cases** 45 patients with variety of SCC seen at H&N tumor clinic • status of necks after dissection: 70% N0, 19% N1, 11% N2 **Methods** • visual interpretation of PET and calculation of SUV for lymph nodes showing increased FDG uptake • CT, clinical exam, and PET results compared to histopathology **Study design limitations** blinding of diagnostic test interpreters not noted	**Test characteristics: cervical node involvement** • PET: *Se = 83%; *Sp = 82%; accuracy = 82% • CT: (insufficient information provided to calculate Se, Sp, PPV, NPV); accuracy = 82% • clinical exam: (insufficient information provided to calculate Se, Sp, PPV, NPV); accuracy = 71% **Agreement of PET and CT** • in 84% of cases • where did not agree, CT more often correct re pathology but PET helped to clarify equivocal CT results **Authors' comments** • CT had lower false negative results than reported in literature; attributed to advances in CT imaging and resolution • FDG use in PET will always be associated with relatively high false-positive rates due to metabolic activity of reactive nodes • PET does not provide anatomic information necessary to surgeons • PET helpful when CT equivocal but cost and information yield of PET compared to CT argue against routine clinical use of PET
Laubenbacher, et al., 1995 *Technical University of Munich, Germany*	**Purpose** • to assess correlation between FDG uptake in primary tumors and histologic grade • to assess contribution of FDG PET to diagnostic accuracy in preoperative assessment of primary tumor and lymph node status • to determine whether attenuation correction is necessary for detection and staging of tumors with PET **Cases** 22 consecutive patients referred for surgery for SSC • range of stages, node status, grade in 17 patients at surgery • histopathologic confirmation in 5 patients with inoperable tumors not obtained **Methods** • whole-body PET performed after overnight fast; blood glucose levels recorded • qualitative (implied) and quantitative analysis of PET images • all patients had MRI, endoscopy, and histopathologic diagnosis/grading of tumors **Study design limitations** • blinding not noted for qualitative image analysis • surgeons had access to PET information and completeness of cervical dissections not reported (work-up bias?) • size criteria only were used for MRI diagnosis of node involvement, which may have decreased Se and Sp compared to diagnosis using additional criteria (e.g. central inhomogeneity)	**FDG uptake** • all primary tumors visualized on PET • no statistically significant difference in SUVs for primary tumor (range, 2.0 - 13.8) vs lymph nodes (range, 1.4 - 11.4) • no plateau in FDG uptake within 60 minutes post-injection • no significant correlation between FDG uptake and blood glucose levels, lesion size, or histologic grade • no significant differences between attenuation-corrected and noncorrected images for staging **T staging** • all tumors clearly visualized with PET, MRI, endoscopy • best results in endoscopy (correct staging in 10/17 cases) • MRI and PET each correctly staged 7/17 cases and overstaged ≈ 50% of cases **N staging** • 521 nodes assessed at surgery in 17 patients (34 neck sides) - 83 positive, 438 negative for metastases - 18 neck sides positive, 16 negative • individual node analysis: - PET: Se = 90%; Sp = 96%; PPV = 80%; NPV = 98% - MRI: Se = 78%; Sp = 71%; PPV = 34%; NPV = 95% • neck side analysis: - PET: Se = 89%; Sp = 100%; PPV = 100%; NPV = 95% - MRI: Se = 72%; Sp = 56%; PPV = 65%; NPV = 64% **Authors' comments** abbreviated protocol with emission scans without attenuation correction appears to fulfill clinical requirements

Study	*Patients/Methods*	*Results/Comments*
Lapela, et al., 1995 *University of Turku, Finland*	**Purpose** • to estimate quantitative FDG uptake values that would suggest the recurrence of head and neck cancer strongly enough to justify surgery • to compare visual, static, and kinetic analyses of FDG uptake in differentiating malignant and benign lesion with patients with previously treated H&N cancer **Cases** 15 patients who presented to otolaryngology department for evaluation of suspected recurrence of SCC after surgery and/or radiation therapy • 2/15 received second PET study for second recurrence **Methods** • blinded, independent visual analysis of 17 PET images by 3 investigators • PET images graded as clearly malignant, suspect, or negative • ROIs defined and SUVs calculated • SUVs used in static and kinetic analyses • CT performed in 13/15 patients and interpreted by one blinded radiologist	**Histopathology** 25 regions in 17 PET studies: 16 malignant, 7 not malignant (2 left out of analyses because PET and histology negative at time of study but recurrence documented within 6 months) **Interobserver variation** • agreement among all 3 PET readers for 20/25 regions • 2/3 readers agreed on remaining 5/25 regions **PET characteristics: blinded visual interpretation** • malignant + suspect lesions = positive: Se = 94%; Sp = 43% • malignant only = positive: Se = 88%; Sp = 86% **Quantitative analysis of PET** • median SUV of benign and malignant lesions significantly different (p = .008) • median regional metabolic rates also significantly different (p = .002) • at SUV = 5.74 cut-point, Se = 75% • at metabolic rate = 15.4 µmol/100g/min cut-point, Se = 86% **CT characteristics: blinded interpretation** •18 regions analyzed • Se = 92%; Sp = 50% **Authors' comments** • complex static or kinetic modelling provides no clear advantage over SUV or regional metabolic rates • SUVs at different institutions may not be directly comparable • quantitative analysis of small lesions (compared to PET resolution) should be performed with caution • PET false-positives attributed to reactive nodes
Benchaou, et al., 1996 *Geneva University Hospital, Switzerland*	**Purpose** to compare the results of PET, CT, and cervical node palpation in N-staging prior to surgery **Cases** 40 SCC; surgery indicated in all patients • 38 primary SSC, stages T1-3 • 2 unknown primary **Controls** 8 with benign or other tumors; surgery indicated in all patients • 6 benign neck masses • 2 cervical lymphoma **Methods** • all patients received clinical exam, CT, PET, endoscopy, surgery with neck dissection (9 node groups/neck side; 4 bilateral and 44 unilateral dissections) and histopathologic confirmation of tumor type and node status • blinded reading (PET qualitative/semi quantitative with lymphoid tissue as reference) of each type of test by certified specialist	**Node status** • 468 node groups examined (54 positive, 414 negative) • 23 patients N0 (15 SSC, 8 other/benign) • 25 patients N1 or N2 **Operating characteristics of tests** • PET: Se = 72%; Sp = 99%; accuracy = 96%; PPV = 89%; NPV = 99% • CT: Se = 67%; Sp = 97%; accuracy = 93%; PPV = 74%; NPV = 95% • Palpation: Se = 61%; Sp = 97%; accuracy = 93%; PPV = 72%; NPV = 95% **Statistical tests** • Se of PET significantly higher than Se of palpation (p = 0.03) • Se of PET equivalent to Se of CT (p = 0.25) • Sp of all tests equivalent (p = 1) • PPV of PET significantly higher than palpation (p < 0. 05)

Abbreviations:
SCC, squamous cell carcinoma
H&N, head and neck
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value
RT, radiation therapy
ROI, region of interest
SUV, standardized uptake value = (tissue activity x weight)/ injected dose

* indicates calculated by MDRC TA Program from data supplied in published article

Table 5 Therapeutic efficacy of FDG PET and anatomic imaging in detecting cervical lymph nodes positive for cancer and potential impact on decision to perform neck dissection

Notes *The study in the table does not meet the evidence-based medicine requirement for blinding; sensitivity and specificity should be interpreted with caution.*

Case series (Level V evidence).

Study	*Patients/Methods*	*Results/Comments*
Braams, et al., 1995 *University Hospital Groningen, The Netherlands*	**Purpose** to investigate usefulness of PET in identifying lymph node metastases, compared to clinical and MRI findings **Cases** 12 patients presenting to H&N oncology group for evaluation of SCC at variety of primary sites **Methods** • whole body PET, MRI, clinical palpation for nodes, and histologic confirmation of node status for all patients during radical or modified radical neck dissection • PET images analyzed visually by two observers at same time • ROIs drawn and SUVs calculated • characteristics of tests calculated • false negative and false positive rates for PET and MRI and institutional criteria for elective and obligatory neck dissections retrospectively applied to hypothetical decision in study subjects **Study design limitations** blinding of image interpreters not noted	**Histopathology of resected specimens** • 22 metastatic lymph nodes • 25 reactive nodes •152 normal nodes **Characteristics of tests** • PET: Se = 91%; Sp = 88%; PPV = 48%; NPV = 99%; false positive rate = 52% • MRI: Se = 36%; Sp = 94%; PPV = 44%; NPV = 92%; false positive rate = 55% **SUV analysis** • metastatic node SUV = 2.5 ± 0.8 • reactive node SUV = 2.6 ± 1.4 (difference between reactive and metastatic nodes not significant) • normal node SUV = 1.0 ± 0.3 (difference between normal and metastatic/reactive nodes significant, $p < 0.001$) **Therapeutic efficacy: perform neck dissection?** • PET: dissection would have been performed in all patients with metastatic disease, and 5 patients would have received unnecessary dissections (false positives) (79% correct decisions) • MRI: 4 patients with metastatic disease would not have received dissections (false negatives), and 4 patients would have received unnecessary dissections (false positives) (66% correct decisions) **Additional findings and authors' comments** • PET false negatives attributed to small size of nodes (< 4 mm) or low SUV and partial volume effect • MRI false negatives in nodes < 10 mm • problem with PET is distinguishing metastatic and reactive nodes (high false positive rate); SUVs provided no additional diagnostic value over visual analysis; additional method to improve false positive rate desirable • sensitivity and specificity depend on number of lymph nodes retrieved during dissections • importance of PET is that no false-negative decisions re neck dissection would have been made

Abbreviations:
SCC, squamous cell carcinoma
H&N, head and neck
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value
RT, radiation therapy
ROI, region of interest
SUV, standardized uptake value

* indicates calculated by MDRC TA Program from data supplied in published article

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Exclusion criteria included:

- number of cases < 12
- duplicated or superseded by subsequent or concurrent study from the same institution
- radiopharmaceutical other than FDG
- gamma camera rather than PET
- insufficient information to judge comparability of case and control groups, details of imaging protocol, whether visual or quantitative analysis of PET data used, or type of PET data analysis used

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